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Baclofen has opposite effects on escalation of cocaine self-administration: Increased intake in rats selectively bred for high (HiS) saccharin intake and decreased intake in those selected for low (LoS) saccharin intake

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ABSTRACT

Rats selectively bred for high saccharin intake (HiS) self-administer more cocaine, escalate their cocaine intake during long access, and reinstate cocaine seeking at higher levels than those bred for low saccharin intake (LoS). The present study was conducted to determine if baclofen, an agonist at the $GABA_b$ receptor, has differential effects on the escalation of i.v. cocaine intake and reinstatement of cocaine-seeking in HiS and LoS rats. HiS and LoS rats self-administered cocaine during a 2-h daily short-access (ShA) phase for 3 days and then long-access (LgA) sessions for 21 days followed by a second ShA phase. One group of HiS and LoS rats received i.p. injections of 2.5 mg/kg baclofen (HiS + B and LoS + B, respectively), and other groups of HiS and LoS rats received saline (HiS + Sal and LoS + Sal) before each daily session. In a second experiment, HiS and LoS rats self-administered i.v. cocaine during 2-h sessions for 14 days followed by a 21-day extinction period. Baclofen (2.5 mg/kg, i.p.) or saline was administered before saline- or cocaine-primed reinstatement sessions. The HiS + B group escalated their cocaine self-administration and had increased cocaine infusions in the post-LgA ShA phase. The LoS + B group self-administered less cocaine throughout the entire LgA period compared to the LoS + Sal or HiS groups. Baclofen attenuated reinstatement of cocaine seeking in both the HiS and LoS rats with no phenotype differences. Thus, baclofen had opposite effects on cocaine intake in HiS and LoS rats during escalation; but similar effects during reinstatement. These results suggest that treatment effects might vary with individual differences (HiS vs. LoS) and the phase of drug-motivated behavior that is modeled.

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1. Introduction

The association of preference for sweetened dietary substances with drug abuse liability has been investigated with rats selectively bred for high (HiS) and low (LoS) saccharin intake (Carroll et al., 2008; Dess et al., 1998), and these studies have characterized HiS rats as drug-prone and LoS rats as drug-resistant. For instance, HiS rats acquire cocaine, heroin (Carroll et al., 2002), and ethanol (Dess et al., 1998) self-administration at faster rates, show greater resistance to the extinction of cocaine-seeking behavior (Perry et al., 2006), have higher cocaine-induced locomotor activity and behavioral sensitization (Carroll et al., 2007), and show more reinstatement of drug-seeking following cocaine priming injections compared to LoS rats (Perry et al., 2006). Additionally, the HiS line displays higher measures of impulsive choice (Perry et al., 2007) and motor impulsivity (Anker et al., 2009b) relative to the LoS rats. Rats screened for high impulsivity using measures such as the five-choice serial reaction time task or the delay discounting procedure are more vulnerable to addictive behaviors across multiple aspects of animal models of human drug addiction relative to rats screened for low impulsivity (Anker et al., 2009b; Belin et al., 2008; Perry et al., 2005). Taken together, the overlap of reciprocal behavioral traits shown by HiS and LoS rats with other phenotypes exhibiting high and low proclivity for drug self-administration suggests that the HiS and LoS rats are ideal models of genetically-mediated drug addiction-prone and -resistant behavior, respectively, in the human population.

While a number of rodent behavioral phenotypes have been developed and tested for their drug abuse liability across several critical phases of the addiction process, little attention has been given to the responsiveness of rats with these individual differences to treatments for drug abuse. Phenotypic behavioral markers such as sweet preference may be predictive of addiction treatment receptivity in humans. Therefore, a potential utility of the HiS and LoS lines is in investigating treatment models during critical phases of drug abuse such as

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escalation (bingeing). During periods of short access (ShA, 1–2 h per day) rats maintain stable intake, while under long access conditions (LgA, ≥6 h per day) they typically increase daily drug intake over extended periods. Self-administration under conditions of LgA is sensitive to individual differences such as sex (Carroll et al., 2005; Roth and Carroll, 2004), impulsivity (Anker et al., 2009b), and sweet intake, such as that displayed by the HiS vs. LoS rats (Perry et al., 2006) that will be used in the present study. For example, HiS rats escalated their drug intake during LgA to cocaine relative to the LoS rats, while there were no phenotype differences during ShA. This gradual increase in consumption is proposed to be a critical component that accounts for the transition of controlled drug use to uncontrolled binge use and addiction, and it is thought to be mediated by dramatic shifts in mesolimbic reward system functioning (Koob and Volkow, 2010). The escalation model is invaluable for understanding one of the most important aspects of addiction, yet only a few studies have addressed the use of treatment agents during this phase (e.g., Hansen and Mark, 2007; Specio et al., 2008), and none have evaluated individual differences using selective breeding models.

Similar to the escalation model, reinstatement (relapse) is another phase of human drug addiction that has yielded individual differences in responding. For example, female (vs. male) rats (Lynch and Carroll, 2000), rats screened for high (vs. low) measures of impulsivity using a delay discounting procedure (Perry et al., 2008), and HiS (vs. LoS) rats (Perry et al., 2006) showed elevated reinstatement of cocaine-seeking behavior compared to their low-performing counterparts. Also, like escalation, reinstatement models a critical phase of human drug addiction in which individual differences in treatment receptivity have not yet been assessed.

In the present studies, HiS and LoS rats were compared on escalation of cocaine intake and during the reinstatement of cocaine-seeking behavior while treated with a pharmacological intervention, baclofen, a potent agonist at the $GABA_B$ receptor that has been used for alcohol and cocaine dependence (for review, see Karila et al., 2008; Leggio et al., 2010; Roberts, 2005; Smith et al., 2004). In rats, baclofen dose--dependently attenuated discrete contextual cue- and cocaine-primed reinstatement (Campbell et al., 1999; Filip and Frankowska, 2007), cocaine sensitization (Frankowska et al., 2009), maintenance of i.v. cocaine self-administration (Campbell et al., 1999), and cocaine-induced dopamine release in the nucleus accumbens (Fadda et al., 2003). In another study, baclofen pretreatment reduced the reinstatement of cocaine-primed behavior in baboons (Weerts et al., 2007).

The effectiveness of baclofen in human populations, however, has been mixed. In a preliminary open-label trial, baclofen (20 mg, t.i.d) reduced cocaine craving and use compared to placebo (Ling et al., 1998). In another study baclofen (60 mg/day) reduced cocaine self-administration, but it failed to alter cocaine's positive subjective effects in non-opioid dependent volunteers (Haney et al., 2006). Despite the mainly promising results of these earlier studies, a recent multi-site, double-blind trial failed to show an effect of baclofen (60 mg/day) on self-reported abstinence or negative urine screens compared to placebo in individuals suffering from severe cocaine addiction (Kahn et al., 2009).

One possible reason for incongruent results from experiments that test treatment drugs for stimulant addiction, like baclofen, is that treatment receptivity may be genetically mediated. Individual differences (male vs. female) have been found in baclofen treatment receptivity, with female rats showing a greater baclofen-induced decrease in the acquisition of cocaine self-administration relative to treated males (Campbell et al., 2002). This is of particular interest, as female rats generally have faster rates of cocaine acquisition relative to males (Lynch and Carroll, 1999). Additional clinical and preclinical research has further identified females as generally more drug prone than males (Becker and Hu, 2008), yet initial results suggest that females are more receptive to treatment than males, possibly due to a rate-dependent effect (Carroll and Anker, 2010).

The goal of this study was to determine if baclofen differentially affects escalation and reinstatement of cocaine-seeking behavior in HiS and LoS rats. These two models of drug abuse represent transition states of drug-taking (escalation) and drug-seeking (reinstatement) aspects of behavior, and are differentiated by high vs. low levels of baseline intake, respectively. As the HiS rats are more prone to drug seeking than LoS rats, and based on initial findings with male and female animals and enhanced treatment effects in females vs. males, it was hypothesized that HiS rats would show a greater decrease in escalation and reinstatement of cocaine seeking following baclofen administration compared to LoS rats. Also, previous research has shown that, following a prolonged period of LgA, rats earn more infusions during a subsequent ShA period relative to the ShA phase that preceded it (Perry et al., 2006). Therefore, HiS rats treated with baclofen were expected to show a greater reduction in post-LgA ShA cocaine intake compared to LoS rats treated with baclofen. Another hypothesis was that baclofen would reduce cocaine-primed reinstatement responding more in the HiS relative to the LoS rats.

2. Methods

2.1. Subjects

Sixty-two experimentally naïve adult female rats selectively bred at the University of Minnesota (Carroll et al., 2002) from Occidental HiS and LoS lines (Occidental College, Los Angeles, CA) were used in this study. Male rats were initially included in this study; however, as previously shown in Carroll et al. (2002), all but one male LoS rat failed to acquire cocaine self-administration. Phenotypic differences were the primary interest in the present study, and HiS and LoS females were used exclusively because they display a wider range of saccharin intake and behavioral measures compared to HiS and LoS males (Carroll et al., 2008). Rats weighed between 278 and 326 g at the start of the experiment and were between 90 and 120 days old. The HiS and LoS lines were cultivated through breeding pairs based on extreme saccharin phenotype scores with no sibling, half-sibling, or first cousin matings. Phenotype score was derived from a 24-h two-bottle test (see Badia-Elder et al., 1996 for details) in which consumption of 0.1% saccharin solution was assessed relative to previously attained 24-h water intake and body weight [saccharin score = (saccharin ml − water baseline ml, divided by body weight, × 100)]. Table 1 shows group numbers, body weights at the beginning of study, daily food and water intake, and saccharin scores.

Rats were bred and pair-housed in plastic cages with ad libitum access to rat pellet chow (Purina Mills, Minneapolis, MN, USA) and water prior to the experiment. The humidity, temperature (21–23 °C), and light–dark cycle (12 h–12 h; lights on at 6:00 a.m.) were all regulated.

Table 1
Experimental group information.

Group	*n*	Weight (g) (±*SEM*)	Daily food intake (g) (±*SEM*)	Daily water intake (g) (±*SEM*)	Saccharin phenotype score[a] (±*SEM*)
Escalation					
HiS + B	8	326 (±11)	16.1 (±0.1)	41.3 (±2.9)	22.8 (±4.6)[b]
LoS + B	9	284 (±11)	15.9 (±0.1)	36.1 (±1.8)	11.6 (±6.3)
HiS + Sal	8	285 (±8)	15.8 (±0.1)	43.3 (±5.2)	25.4 (±10.2)[b]
LoS + Sal	10	282 (±10)	15.9 (±0.1)	34.4 (±1.5)	9.2 (±7.2)
Reinstatement					
HiS	14	283 (±5)	15.9 (±0.1)	42.0 (±3.3)	18.1 (±3.3)[b]
LoS	13	278 (±6)	15.9 (±0.1)	37.7 (±5.6)	0.9 (±3.6)

[a] Saccharin phenotype score = {[24-h saccharin intake (ml) − average water intake (ml)/weight (g)] × 100} (Dess et al., 1998).
[b] Indicates that after combining saccharin phenotype scores between both experiments HiS rats had significantly higher scores compared to LoS rats ($p < .01$).